

**IN THE UNITED STATES DISTRICT COURT FOR THE
MIDDLE DISTRICT OF TENNESSEE
NASHVILLE DIVISION**

RUTH SMITH, Individually and as Widow for the)	
Use and Benefit of Herself and the Next of Kin of)	
Richard Smith, Deceased,)	
)	
Plaintiff,)	
)	Civil No. 3:05-0444
v.)	Judge Aleta A. Trauger
)	
PFIZER INC., <i>et al.</i> ,)	
)	
Defendants.)	

TESTIMONY OF ALEX P. RUGGIERI, M.D.

My name is Alex Ruggieri. I live in Simi Valley, California. I have a Master's Degree in Public Health and a Doctor of Medicine Degree. I am a physician and am board-certified in Internal Medicine and Rheumatology. I currently work as the Managing Medical Director in Anthem Care Management, Pharmacy and Therapeutics, Senior and State-Sponsored Business at Wellpoint in Thousand Oaks, California. Since joining the company, I have been involved in the oversight of the development of drug formularies and drug utilization management practices. This has required a thorough understanding of the benefits and risks of drugs in clinical use.

I attended Georgetown University from 1969 to 1973, obtaining a Bachelor of Science degree in Chemistry. I then attended the Johns Hopkins University School of Public Health from 1976 to 1977, where I received a Master of Health Science degree in Public Health. I completed medical school at Georgetown University and received my Doctor of Medicine degree in 1980 with honors. I graduated from medical school as a member of the Alpha Omega Alpha Medical Honor Society. I successfully completed post-graduate medical training in Internal Medicine and Rheumatology. I completed my Internship and Residency in Internal Medicine and my Post-

Graduate Fellowship in Rheumatology and Immunology at the Medical University of South Carolina. A copy of my Curriculum Vitae includes my educational and professional experience and is marked as **Exhibit 7415**.

Subsequently, I have accumulated over 16 years of clinical experience in private practice and academic medicine where I treated a variety of diseases and conditions in patients typical for an internal medicine practice and specialized in rheumatic disorders, most of which are chronic, incurable, progressive, and associated with both psychological and physical distress. Working with patients who had chronic, debilitating and dire diseases for which treatments were often very limited or ineffective led me to appreciate the impact on patients, and the desperate need to explore any and all available therapeutic approaches especially when conventional treatments failed. The majority of my patients experienced significant depression as a result of their condition at least multiple times during the course of treatment. The clinical knowledge and experience I built over this period enables me to evaluate and understand the details and complexity of individual case reports of adverse drug events and provide accurate assessment of causality in the context of the clinical background in each case. One of the conditions I have treated is neuropathic pain, and like the patients I treated with rheumatic disorders, patients with neuropathic pain were difficult to treat because of the limited number of treatment options. I have prescribed Neurontin to patients with neuropathic pain and have found it to be effective and safe in treating neuropathic pain patients.

The academic training I completed for my Master's of Health Science degree included and required the development of analytical skills in epidemiology and biostatistics. That training was further supplemented by additional post graduate training in epidemiology and biostatistics and statistical computing required as part of National Library of Medicine Fellowship Program

in Medical Informatics, which is a medical scientific discipline involving the design and use of data in electronic databases to draw medical conclusions. Subsequent to this training I received an academic appointment in the Department of Biomedical Informatics at Mayo Clinic where I received an NIH R01 research grant as principal investigator for a three-year research project. My skills in scientific methods which formed a basis for receiving this award are the same that are applied in studying the issues presented in this case.

I have designed information systems and directed data management activities for the purpose of creating clinical data warehouses for research and knowledge discovery. I helped develop logic based medical terminologies for clinical electronic records that enabled concept based search and retrieval of data. I have developed expertise in data management and data analytics and in doing so practiced and applied epidemiological methods and techniques. I held an appointment as Assistant Professor in the Department of Health Sciences Research at Mayo Clinic and performed research and taught doctoral level students. This case involves the recognition and appropriate analysis of electronic databases, such as the adverse event and clinical trial databases found at FDA and Pfizer, which hold data relevant to drug safety questions. My training and experience in medical informatics specifically pertains to this type of issue.

Subsequent to this experience I held the position of Medical Director for Global Safety, and Director for Information Management and Strategy in the department of Global Regulatory and Safety at Amgen Inc., a large pharmaceutical company. I directed and managed safety surveillance activities for a therapeutic area involving multiple biologic therapeutic agents and my activities extended across pre- and post-market approval for these products. A biologic agent is a naturally-occurring molecule that is engineered to act in a certain way in the human body for

therapeutic purposes. I directed pharmacovigilance activities for several products and interacted with global regulatory agencies and global labeling groups for purposes of safety knowledge discovery and appropriate safety conveyance. Pharmacovigilance is the science of collecting, monitoring, assessing and evaluating information from healthcare providers, consumers and patients on the potential adverse effects of medications, to identify the best information available relevant to potential hazards associated with medicines to prevent unnecessary harm to patients. As I will discuss later, companies are required to conduct pharmacovigilance activities, which are monitored and audited by regulatory authorities, such as the FDA. It is my opinion that Pfizer appropriately conducted pharmacovigilance activities in connection with Neurontin. In fact, its practices met the accepted standards and regulatory requirements for this activity.

My pharmaceutical industry experience has enabled me to understand the drug development process and the strengths and limitations of the various data sources for the purpose of drawing inferences regarding safety issues. I developed, implemented, and executed signal detection and analysis methodologies, pharmacovigilance plans and risk management plans. I have identified safety issues and communicated them to patients, providers, regulators, business partners, and colleagues at my company. I have studied and performed drug safety issue analyses and have studied and applied the scientific principles, analytic methods, information and data management techniques that serve as a foundation of those analyses.

I have reviewed numerous documents relating to Neurontin. These documents include, but are not limited to documents from the Neurontin IND, NDA and sNDAs; the FDA medical officer's reviews of the NDAs and sNDAs; Neurontin labeling; internal company documents regarding monitoring of post-market drug safety of Neurontin; the company's submissions to FDA regarding analyses of suicidal behavior; 2008 Advisory Committee transcript and

supporting documents; depositions of certain fact witnesses; and relevant journal articles and other scientific publications. I am relying on my professional training and experience in reviewing these materials. I have also reviewed the reports, declaration, deposition testimony, and materials considered by plaintiffs' expert Cheryl D. Blume, Ph.D. I also reviewed expert reports and materials considered by other defense experts.

I was asked to evaluate and address (1) the scientific principles and methods for acquiring and evaluating evidence on which scientific assessments and conclusions relating to causation in drug safety matters are based; (2) whether there is reliable scientific evidence to establish an association between gabapentin and suicide or suicide attempt; (3) whether the clinical evidence that existed or emerged over time supported a warning, precaution or contraindication in the Neurontin package insert related to any increased risk of suicide or suicide attempt; (4) standards of safety and pharmacovigilance management practices undertaken by the Pfizer defendants; and (5) the relevance and scientific validity of assertions made by the plaintiff that gabapentin causes suicide or suicide attempt.

My opinions to a reasonable degree of scientific certainty, which are based on my evaluation of the materials and my education, training and experience, are summarized on the current slide [**SHOW POWERPOINT HERE (DR. RUGGIERI'S OPINIONS)**], and are as follows:

- (1) Pfizer and Warner-Lambert acted reasonably and complied with regulatory requirements in monitoring the safety of Neurontin.

- (2) The information available to Warner-Lambert and Pfizer has consistently failed to support an association or reveal any signal of potential increased risk for depression or suicidal behaviors in patients taking Neurontin.
- (3) No signal emerged sufficient to raise special safety concerns in the off-label use of Neurontin.
- (4) The Neurontin labeling adequately conveyed necessary information to prescribers regarding the risks and benefits of the medicine.

In order to explain the basis of my conclusions, let me provide you with some background information. A signal is any collection of information that leads to a suspicion of a potential relationship between a drug and an event. A signal is a hypothesis, which may give rise to a scientific inquiry to establish an association between an event and use of a drug, but it is not a conclusion and is not scientific evidence in and of itself. A signal, itself, is not usually sufficient to provoke labeling decisions or actions. Signals may be monitored through the capture and review of individual adverse event reports submitted to the company or regulatory spontaneous adverse event reporting databases, or through data mining methods applied to collections of data pertaining to medication use and medical events. As explained in **Exhibit 7403**, which is the March 2005 FDA Guidance on Good Pharmacovigilance Practices, recognizes that data mining techniques to perform signal detection are not fully developed. As such, they are not yet considered part of routine pharmacovigilance. Data mining involves the use of computer programs to analyze large quantities of data obtained from information submitted to the company or the FDA. Data mining does not, and cannot, establish a causation relationship. However, it can detect patterns that may lead one to suspect an association between a drug and an event. These patterns, if valid, must be further explored with more rigorous

scientific methods in order to address questions of causation. It is important to remember that when assessing issues of causation with any adverse event and a drug, data mining is not a tool for making judgments about whether a medicine causes an adverse event. The FDA has stated repeatedly that spontaneous adverse event reports, the source information for much of the data mining discussed in this case, are not reliable or sufficient to determine a possible causative relationship between suicidal behavior and use of Neurontin.

It is widely accepted that the mere identification of a signal does not in any way constitute or establish a causal relationship between an adverse event and use of a medication, nor is it or should it be used alone as a basis for issuing a warning. The mere finding of a signal does not negate the findings of a randomized controlled clinical trial, known to be the source of the strongest form of evidence regarding the effects of drugs, or other epidemiological factors. The identification of a signal outside of a controlled scientific observational setting provides insufficient evidence to establish a causal relationship of a medical event. Whenever a legitimate signal is identified, further analysis must be undertaken to determine its meaning.

When sufficient evidence exists that the signal is real, one may form a hypothesis about a relationship between use of a drug and a clinical event. More definitive methodologies must then be employed in order to draw conclusions about the relationship and to guide decisions whether to redefine the safety profile of the medication. Clinical judgment is critical to determining whether a single spontaneous adverse event report by a provider or other individual constitutes a meaningful signal and whether a finding of an increase in such reports of an event is true. In a 2005 article by Brian Strom in the Journal of the American Medical Association, which is labeled **Exhibit 987**, Strom states that **[SHOW POWERPOINT HERE (CLINICAL JUDGMENT NECESSARY TO INTERPRET SIGNAL)]** “Proper interpretation [of an

adverse event report] requires clinical judgment even before one even considers there to be a signal,” and in his textbook, Pharmacoepidemiology, he states that “...any such signals must be confirmed by detailed evaluation by skilled clinicians and epidemiologists of the case reports that generated the signal.”

Based upon my review of the record in this case, I am familiar with Pfizer’s and Parke-Davis’s pharmacovigilance activities regarding Neurontin, and it is my opinion that the company complied with regulatory and safety standards regarding pharmacovigilance activities sufficient to satisfy global regulatory requirements.

Under the applicable FDA regulations, an “unexpected” adverse drug experience is any adverse drug experience that is not listed in the current labeling documents for the drug product. Once an adverse event is listed in the labeling documents, it is designated “expected.” But, this designation is not literal and does not mean or imply that the event is causally related to use of the drug. The designation listed merely means there are known reports, valid or invalid, that the event occurred while a patient was taking the drug. **[SHOW POWERPOINT HERE (SAMPLE MEDWATCH FORM)]**. This slide shows an example of a MedWatch report form, which is a form that doctors and pharmacists use to report adverse events to FDA. You will note that this form that is created by FDA states that the filing of a report does not mean that the drug caused the event.

To facilitate organization and indexing, adverse events are coded using standard coding dictionaries and terminologies. For example, any given patient may describe the same symptoms experienced on a drug in different ways. For example, a patient could describe an upset stomach as “queasy,” “sick to my stomach,” or “I want to throw up.” These verbatim descriptions from patients and physicians that are reported to a drug company are reviewed and coded or placed in

conceptual “buckets” for organizational purposes. These buckets are labeled using what are called “preferred terms” in order to capture the commonality of patient expressions. An example of a preferred term in this instance could be “nausea.”

At the time Neurontin was first being evaluated by the FDA for the indication of treating epilepsy in the early 1990’s, the standard coding dictionary of preferred terms was called COSTART and was the standard set of preferred terms or words routinely used by FDA and industry to organize adverse event reports. It was broadly recognized by experts that the COSTART dictionary was not complete. That is to say it had an insufficient collection of terms or formal words to fully describe and categorize adverse event reports. Because there was a lack of formal preferred terms to represent the spectrum of adverse events seen in Neurontin clinical trials, Warner-Lambert used an expanded COSTART dictionary. The expanded COSTART dictionary, which is at Appendix B.1 of the Fourth Safety Update and is **Exhibit 7081** , incorporated richer and more diverse terms to more precisely categorize adverse event reports. The expansion and enrichment of the COSTART dictionary ensured greater consistency and accuracy in describing and summarizing adverse events. The use of this modified COSTART dictionary was not only permitted but also was a model for improvements in the COSTART dictionary that occurred later because it enhanced the capture and representation of types of adverse events. Parke-Davis was open and explicit about its use of the modified COSTART dictionary and its use was endorsed by the FDA.

All adverse events reported by patients during clinical pharmacology or clinical studies were reported on case report forms, or CRFs. In a January 28, 1993 contact with the FDA, which is labeled **Exhibit 7123**, the record of the contact stated: “When we briefly reviewed some

of the adverse events . . . that had the COSTART term modified, Dr. McCormick seemed to agree with what we had done.”

In 1997, the FDA switched to a new coding dictionary called MedDRA, which modeled and included similar changes that Parke-Davis incorporated into the modified COSTART dictionary. MedDRA is still being used today and is continually being expanded as a coding dictionary for adverse events.

The change and evolution in coding dictionaries unavoidably impacts the coding of suicidal events. For example, “suicide” was coded as “suicide attempt” in COSTART with a designation of “outcome as death” elsewhere in the adverse event report form, but is now represented now as “completed suicide” in MedDRA. Despite the change in coding the equivalence of the concepts is maintained. “Suicide attempt” was coded as “suicide attempt” in COSTART, without the outcome of death designation, whereas the term “suicidal” in the modified COSTART corresponded to “suicide attempt” in MedDRA, with preservation of the concept. Changes in coding, after the introduction of the MedDRA dictionary, which have evolved over time, attempt to provide more precise and consistent classifications of adverse events. It is my experience that regardless of the coding dictionary used after 1993, companies were adequately able to monitor potential safety issues raised by these reports because the dictionaries contained equivalent terms or words.

Following FDA’s initial approval of Neurontin in 1993, the company continued to monitor the safety of the drug. As required by regulators in the U.S. and overseas, the company made regular reports of safety data that the company had accumulated to the appropriate regulatory agencies. The documents that contain these periodic safety reports are called Periodic Safety Update Reports (PSURs), and typically are directly submitted to foreign regulatory

authorities but are also often communicated to the FDA, are submitted on a regular basis and were in this instance by Warner Lambert covering periods 5/22/1995 – 11/22/1996, 2/2/1997 – 12/31/1997, 8/8/1998 – 1/21/1999, 2/2/1999 – 7/31/1999, 8/1/1999 – 12/31/1999, 8/1/2000 – 1/31/2001, and 2/1/2001 – 7/31/2001. In addition, the company sent 1-year and 5-year PSURs to the FDA in 2004. Periodic Reports were also sent to FDA per the regulations on a regular basis from 1994 onward. I reviewed these PSURs and Periodic Reports, and these reports met industry standards for format, content and thoroughness. These PSURs or Periodic Reports cover a broad range of reported adverse events.

In addition to foreign regulatory authorities, PSURs were submitted to the FDA. In **Exhibit 7175**, which is an April 27, 2004 report of a teleconference with the FDA, the FDA requested a 1-year PSUR (covering 2/1/2003 – 1/31/2004) and a 5-year PSUR (covering 2/1/1998 – 1/31/2003). The FDA specifically requested that Pfizer denote specific sections in each PSUR, including: clinical trial and literature cases, behavior related events, death as an outcome, overdose, and selected topics from the psychiatric disorders. The FDA was able to review data on these specific topics.

The company also reviewed adverse events being reported for Neurontin through the use of a Product Maintenance and Pharmacovigilance (PMP) Team and Core Working Groups (CWG). Each CWG is a cross-functional team composed of key medical, regulatory, drug safety, and risk management personnel, responsible for close periodic monitoring of all significant adverse event reports, as well as ‘designated medical events’ with the respective product. The CWG was a proactive pharmacovigilance activity where possible signals or concerns from adverse event reports are reviewed by a combination of drug safety professionals. This group was given the authority to make decisions to pursue and perform more focused and

intensive analysis and consideration of AEs that may meet criteria for a definite safety signal or concern. An overview of PMPs meetings and activities can be found in **Exhibit 7267**, the minutes from the first PMP meeting, which took place on May 9, 2001. PMPs, which include representatives from Safety Evaluation and Epidemiology, Worldwide Safety, the Worldwide Team (medical and marketing), Regulatory Strategy, Clinical Safety and Risk Management, Clinical Development, Regulatory Quality Assurance, Clinical Data Operations, Legal, Global Medical Information, Outcomes Research, and Corporate Media Relations, “meet at regular intervals to facilitate communication and assure a multidisciplinary approach to ongoing pharmacovigilance and communication of safety information.” The first PMP meeting largely served information exchange purposes and included presentations on summaries of the history of Neurontin and its safety profile, as well as updates on more current issues. **[SHOW POWERPOINT HERE (JUNE 7, 2001 MEMO ON FIRST PFIZER PMP MEETING)]** The objective was also to explore any possible safety signal candidates in the database involving gabapentin use for neuropathic pain.

On July 12, 2002, Chris Pacella, a Pfizer employee, who was part of the Labeling Core Working Group (LCWG) of the Neurontin PMP, emailed the rest of the LCWG a summary of postmarketing reports for Neurontin in order to conduct a review of all the adverse events. This email and the attachment to the email are labeled **Exhibit 7323**. The minutes from the 7/25/02 LCWG meeting, which are labeled **Exhibit 7273**, state that adverse events selected for review by the labeling CWG for possible addition to the gabapentin labeling were so called “unlabeled”, that is adverse events that had not been reported before, and which met *one or more* of the following criteria, which are displayed on the current slide **[SHOW POWERPOINT HERE (PFIZER REVIEWED ADVERSE EVENTS)]**: 1) reporting frequency of $\geq 1\%$, 2) medically

significant, 3) characteristic of a drug-induced adverse reaction in general, and 4) pharmacologically plausible. An adverse event only had to meet one of the criteria. For example, if medically significant, it would still be reviewed even if its reporting frequency did not meet the 1% threshold. In fact, of the 65 adverse events chosen for review, only six events had reporting frequencies of at least 1%. The reporting frequencies for the remaining types of adverse events were all below 1%. The summary sent to the LCWG team by Chris Pacella included data on suicide, specifically 26 suicide attempts, or 0.24%. Chris Pacella testified at his deposition that ALL events on the summary, not just the ones greater than 1%, were considered under the mentioned criteria. This data was reviewed by regulatory professionals, pharmacists and medical professionals who comprised the LCWG. A number of terms were added to the Neurontin label as a result of this review, but suicide attempt was not one of the adverse events added because, as Mr. Pacella testified, after scientific and medical consideration it was determined that no changes to the Neurontin labeling regarding suicide attempt were necessary.

In addition to PSURs and Periodic Reports, the company analyzed the safety experience of Neurontin in 2001. In 2001, when the company was seeking a new indication for neuropathic pain, the company undertook a review of adverse events, an overview of which is in **Exhibit 7161**, which is a March 15, 2001 proposal regarding the review. **[SHOW POWERPOINT HERE (PFIZER ANALYSIS OF ADVERSE EVENTS IN OFF-LABEL USE POPULATIONS IN 2001)]**. This was a “[r]eview of events of relevance in the neuropathic pain population. The intent was to examine whether there are possible signals of specific adverse events in the neuropathic pain population that may be diluted by the overall population and to assess the strength of any signal.” At the time this analysis was performed, the use of Neurontin in the neuropathic pain population was considered to be off-label. For this analysis, **[SHOW**

POWERPOINT HERE (PFIZER ANALYZES ADVERSE EVENTS IN NEUROPATHIC PAIN POPULATION IN 2001)] because “[p]atients with chronic neuropathic pain may represent a population with a significant amount of co-morbid depression (150 cases) and suicide (15),” the company “looked at [these cases] to include or exclude any significant signal of drug induced depression/worsening depression.” Here, the company is reminding the FDA that patients with chronic conditions such as neuropathic pain commonly suffer from depression regardless of treatment. The findings from this analysis were included in the Integrated Summary of Safety submitted to the FDA in connection with its application to gain approval for a neuropathic pain indication, which is labeled **EXHIBIT 7087**. As you can see on the slide that is currently being shown, **[SHOW POWERPOINT HERE (PFIZER’S CONCLUSIONS ON ANALYSIS OF NEUROPATHIC PAIN ADVERSE EVENT DATA IN 2001)]** the company found that: 1) the overall adverse event profile of Neurontin was “consistent with the current prescribing information for [Neurontin] in the treatment of epilepsy;” 2) “the adverse event profile in the neuropathic pain dataset was similar to the dataset comprised of other indications and to the current prescribing information for [Neurontin] in the treatment of epilepsy”; and 3) “no significant signals were detected in the neuropathic pain dataset that would indicate adverse events causally related to [Neurontin] that are novel in terms of their nature or severity.” I have an opinion to a reasonable degree of medical and scientific certainty as to whether a postmarketing safety signal for depression or suicide emerged for Neurontin through 2002. My opinion is that, based on the data in the PSURs, Periodic Reports, and Neuropathic Pain analysis, the postmarketing data through 2002 showed no evidence of any safety signal or alert. After 2002, Pfizer continued to evaluate postmarket safety of Neurontin as I will describe in more detail.

After 2002, additional analyses of the safety of Neurontin were also done in response to a request from the FDA. In 2004, the FDA contacted the company regarding concerns that it had regarding the adverse event of suicidality. Importantly, prior to 2004, plaintiffs' lawyers began to advertise on television soliciting for potential suicide adverse event reports in patients who were prescribed Neurontin and submitted those solicited cases to the FDA's Spontaneous Adverse Event Database. The FDA database was intended to be a database of spontaneous unbiased and unsolicited adverse event reports, hence the designation Spontaneous Adverse Adversity Report Databases. Activities such as advertising and publicity can inject bias into the FDA database and create non scientific data which hampers the ability of FDA and the company to objectively evaluate adverse event reports. Dr. Blume concedes that at least by June 2003, the publicity was such that the adverse event databases were biased by notoriety or publicity. It is my opinion that the adverse event report database for Neurontin was influenced by litigation and subsequent solicitation of reports, the surrounding publicity concerning Neurontin, as well as publicity surrounding safety issues of other medications during this time period.

In 2004, the FDA participated in the design of the protocol for the analysis of adverse events relating to suicidality that was to be completed. The study protocols that were ultimately approved involved a substantial amount of control by the FDA, and included existing data and information by the FDA and Pfizer, indicating that the September 2004 response to the FDA's request contained a sufficiently comprehensive analysis of all suicide-related events. Some specific examples of exchanges between Pfizer and the FDA occurred on April 26, 2004, April 30, 2004, and May 6, 2004. The exchange that I am about to discuss will give you an idea how much care and thought went into this analysis by FDA and Pfizer. Their goal was to create a comprehensive approach to answer the question as to whether the Neurontin safety data

demonstrated a signal or an association to suicidality. The agreed upon method differs sharply from the method used by Dr. Blume in this case.

On April 26, 2004, a teleconference was held between Pfizer and the FDA's Division of Neuropharmacology to discuss reports of suicide in patients taking Neurontin. A report of that FDA contact is at **Exhibit 7174**. Dr. Russell Katz, the director of the Division of Neuropharmacology, asked Pfizer to review the data from controlled clinical trials and open-label studies and post-marketing data for reports of suicide and to submit a protocol for how the data would be ascertained and reviewed for approval. Pfizer received from the FDA the exact preferred list of terms to retrieve adverse event reports. The FDA also asked Pfizer to provide copies of the 5-year and 1-year PSURs.

On April 30, 2004, Pfizer sent a proposed analysis plan to the FDA. The email from Manini Patel of Pfizer regarding this proposal and teleconference details is labeled **Exhibit 7176**. The proposed analysis plan, which is labeled **Exhibit 7177**, detailed the search methodology for analyzing data from the NDA clinical trials (controlled studies and open-label extensions) and post-marketing reports. The proposal provided that: (1) data from clinical trials are in electronic databases or in study reports; (2) the review will be done in a blinded fashion; (3) for studies with no electronic data, adverse event terms from study reports will be reviewed with event terms consistent with certain text strings; and (4) retrieval and analysis of post-marketing data will involve researching the current database (ARISg) for cases reported after June 1, 1995, and the inactive legacy database for cases reported before June 1, 1995. The proposal also provided that the outline for the search strategy for finding data from electronic sources involved analyzing events and investigator terms that are on the slide currently being shown. **[SHOW**

POWERPOINT HERE (FDA SEARCH STRATEGY USED BY PFIZER IN 2004 FOR SUICIDE DATA FROM “ELECTRONIC SOURCES”)]

On May 6, 2004, Pfizer held a teleconference with the FDA to discuss the search plan submitted to the FDA on April 30, 2004. A contact report regarding this teleconference can be found at **Exhibit 7178**. During this teleconference, Dr. Katz provided feedback on Pfizer’s search proposal. Dr. Katz asked that Phase I studies be included in the analysis and looked at separately. He acknowledged that phase I studies are short in duration and involve healthy subjects, but indicated the need to explore if there was a condition independent drug-induced suicide effect. So, the FDA asked for studies that it knew were short in duration and involved healthy subjects.

Pfizer and the FDA continued to develop the study protocol after this, and there were numerous back-and-forth exchanges between FDA and Pfizer through July of 2004. On July 16, 2004, the FDA responded to Pfizer’s responses sent to the FDA on July 2, 2004, and stated: “Your responses are acceptable. We request that you now submit your comprehensive analysis plan proposal to the FDA, integrating all of your responses to our comments and questions into one detailed and comprehensive analysis plan document.” The FDA’s July 16, 2004 response is **Exhibit 7186**. An August 6, 2004 letter, which is labeled **Exhibit 7188**, noted that agreement was reached between FDA and Pfizer on the proposed analysis plan and submitted the final comprehensive analysis plan to the FDA. Pfizer and FDA worked together for period of months to create the most appropriate and comprehensive search protocol to address the question.

The findings of this comprehensive analysis were submitted to the FDA in September of 2004, and these findings are labeled **Exhibit 7191**. Pfizer commented on the background rate of suicide in the population exposed to Neurontin, specifically that patients with disorders for which

Neurontin is used have significantly higher rates of suicide relative to the general population. **[SHOW POWERPOINT HERE (PFIZER 2004 RESPONSE TO FDA REGARDING SUICIDE AND SUICIDE ATTEMPT IN NEURONTIN – IMPORTANCE OF BACKGROUND RATES)]** The literature indicates that the natural risk or background rate for suicide regardless of treatment is higher in patient populations with psychiatric or pain disorders and epilepsy than the rates expected in the general population. Annual rates of suicide in bipolar disorder were the highest among the patient groups reviewed (0.40%), followed by anxiety disorders (0.193%), then epilepsy (0.035%-0.073%) and pain (0.02%-0.05%). This is in comparison to the annual international population rate of 0.0143% and an annual U.S. population rate of 0.011%.

An analysis of the Phase 2-4 clinical studies revealed only two completed suicides: one of the completed suicides was determined by the investigator to be definitely not related to gabapentin, and the other completed suicide occurred six months after Neurontin was discontinued and, therefore, could not have been related to Neurontin use.

An analysis of the Phase 2-4 clinical studies revealed only 12 cases of attempted suicide in patients taking Neurontin (1 in placebo-controlled and 11 in non-placebo-controlled studies). Nine of the 12 cases were considered by the investigator as having an unlikely relationship to gabapentin or as definitely not related to gabapentin, while only three of the 12 cases of attempted suicide in the Phase 2-4 clinical trials were considered to be even possibly related to Neurontin use. It is important to understand that in this analysis, FDA and the company both analyzed suicidal adverse events that were reported.

Results of post market adverse event report analyses stated: “As of 31 March 2004, a total of 17,768 non-clinical study cases have been submitted to Pfizer. A review of gabapentin

non-clinical study cases identified 35 cases of completed suicide, representing a small proportion (0.2%) of the total number of gabapentin cases.” The company stated that no conclusion could be drawn about the 35 suicide reports, because these reports did not contain adequate information to draw such conclusions. For suicide attempts, the company stated that no causation conclusions could be drawn from these cases.

Based on the data submitted in this September 2004 report, **[SHOW POWERPOINT HERE (PFIZER 2004 RESPONSE TO FDA REGARDING SUICIDE AND SUICIDE ATTEMPT IN NEURONTIN – COMPANY’S CONCLUSIONS)]** the company’s conclusion was that “the combined results of a comprehensive search for cases of suicide and suicide attempt among gabapentin clinical trials and postmarketing data across all patient populations did not indicate an increased risk of suicide with gabapentin treatment. The results of this review are consistent with the published literature for suicide in comparable patient populations in which gabapentin has been studied or used.” My opinion to a reasonable degree of medical and scientific certainty is that the findings of the company were correct that these data, as of March 31, 2004, did not indicate a signal for increased risk of suicidal behaviors with Neurontin and that the rates of suicide and suicide attempt found in this study are entirely consistent with the background rates for the disease states of the patient populations taking Neurontin. It is also my opinion that the methods and analytical framework designed by FDA and Pfizer was appropriate and generated accurate conclusions. It is also important to note that after receipt of this information, FDA did not require or recommend any warning pertaining to suicidal behavior or depression in the Neurontin label.

Following the September 2004 submission, in June of 2006, at the request of the FDA and using FDA inclusion criteria, Pfizer submitted the results of its evaluation of Neurontin

clinical trial data for “possibly suicide-related adverse events.” This June 2006 submission is labeled **Exhibit 7207**. The FDA first requested placebo-controlled trial data from Pfizer and other AED manufacturers in a letter dated March 16, 2005, which is labeled **Exhibit 7197**. The FDA requested that Pfizer identify trials from its development program (regardless of whether the indication is approved or not) that met the following criteria: (1) placebo-controlled; (2) parallel arm; (3) short-term (up to six months); and (4) at least 30 patients total. The FDA also stated that “[s]ome trials in epilepsy may have utilized a subtherapeutic dose of a standard AED as a comparator arm. Those trials should be included (if they meet the other criteria described above)”

The choice of controlled clinical trial data by the FDA to conduct their analysis was correct as this type of data represents the gold standard in experimental data of this type. Because of the design of randomized controlled trials, many biases are eliminated and the data are far more reliable. This is especially important when analyzing psychiatric-type events such as suicidality. The FDA confirmed that controlled clinical trial data are the most reliable and most relevant to analysis of suicidality because in 2008, after the FDA AED alert came out, I wrote to the FDA to confirm that postmarketing data were not being used in their 2008 analysis of 11 AEDs. The FDA responded to my inquiry in an email dated April 1, 2008 that is labeled **Exhibit 7392** and is shown on the current slide, **[SHOW POWERPOINT HERE (FDA EMAIL TO RUGGIERI: CONTROLLED TRIALS THE ONLY WAY TO ESTABLISH WHETHER AEDS ARE RESPONSIBLE FOR SUICIDE)]** and stated that “the agency does not believe that spontaneous post-marketing reports can be interpreted appropriately in this situation. Patients taking these drugs have a high background rate of suicidal thoughts/behaviors, and it is not possible to tell from AERS reports, whether the drug caused

them.” The FDA told me that “in the agency's view, the only way to establish whether or not the drugs are responsible for suicidality is to analyze controlled trial data.”

The FDA again commented that postmarket data are not appropriate for this type of analysis at the Joint Advisory Committee Meeting regarding AEDs and suicidality on July 10, 2008. At this meeting, the FDA said that postmarketing spontaneous adverse event data are not appropriate for a study of suicidality in the population of patients taking AEDs, because such patients have a high background rate of suicide. Dr. Katz stated that the FDA “had long ago decided that postmarketing data are not the right data to look at . . . where there is a high background rate of suicidality so defined in these populations,” and that for this type of analysis, “postmarketing data is uninterpretable, and that is why [the agency] went to placebo-controlled trials.” This demonstrates FDA currently recognizes and understands that patients with these diseases and disorders, including neuropathic pain, have an increased risk of suicidal events, which occur by virtue of these conditions themselves regardless of treatment. A transcript of this Joint Advisory Committee Meeting is **Exhibit 7257**. The FDA’s repeated statements regarding the unreliable and un-interpretable nature of postmarketing data are contrary to the assertions made by the plaintiffs’ experts, who use postmarket adverse event report data entirely and solely as a basis to assert in a link between Neurontin and suicidality.

In response to Pfizer’s June 2006 submission regarding controlled trial data and after some back-and-forth communication between the company and the FDA, the FDA responded on December 28, 2005, in a letter that is labeled **Exhibit 7205**, agreeing with Pfizer’s selection of qualifying clinical trials to include in the analysis and asking that Pfizer use this list of studies to identify and further evaluate “possibly suicide-related” adverse events occurring in these trials. In this process, the FDA established the criteria for identifying the possibly suicide-related

adverse events. The FDA, in a March 16, 2005 letter that is **Exhibit 7197**, provided specific search strategies to identify adverse events of interest, verbatim text strings to be used in conducting searches, and specific detailed instructions regarding the preparation of narratives for each adverse event identified, and also noted that all deaths, serious adverse events and “accidental” injuries should be included.

This June 2006 analysis, which is labeled **Exhibit 7207**, included 8829 patients, and “[u]sing the search strategies stipulated by FDA for “Possibly Suicide-Related” adverse events that occurred during the double-blind phase of treatment or within one day of beginning of taper, switching or stopping treatment, 336 possible cases out of 8829 patients were identified.” As shown in this slide from the June 2006 analysis, **[SHOW POWERPOINT HERE (NEURONTIN PLACEBO-CONTROLLED CLINICAL TRIAL DATA)]** a further analysis and classification of the 336 possible cases revealed no cases of completed suicide, no cases of attempted suicide and no cases of “preparatory acts towards imminent suicidal behavior” among Neurontin users. There were two suicidal ideation cases in Neurontin-treated patients, and one suicidal ideation in placebo-treated patients. I have formed an opinion, to a reasonable degree of medical and scientific certainty, as to whether these data suggest an increased risk for suicidal behaviors in Neurontin-treated patients. It is my opinion that these data support the conclusion that Neurontin use does not pose an increased the risk of suicidal behavior or thinking and that Neurontin neither causes nor is associated with an increased risk of suicidal behavior and thinking, completed suicide, suicide attempt, suicide gesture and suicide ideation.

I also have an opinion to a reasonable degree of medical and scientific certainty as to whether the labeling for Neurontin adequately conveyed the appropriate information to physicians regarding suicidal behavior and depression. My opinion is that the information as

conveyed in the label was consistent with that reflected in the clinical trials and there was no basis prior to August 4, 2004, to warn of an increased risk of suicidal behavior or worsening of depression nor is there now. As directed by FDA, and fully consistent with the known safety data, the Neurontin label contained information on depression and suicidality in the “Adverse Reactions” and “Other Adverse Events Observed During All Clinical Trials” sections. Up until December of 2005, the Neurontin label contained the terms “suicidal” and “suicide gesture” as “infrequent” and “rare” adverse events, respectively. I have treated patients that I have considered to be suicidal or to show suicide gestures. As a clinician, “suicidal” is a very broad term that encompasses suicide gesture, suicide ideation, suicide attempt or suicide. A suicidal patient has either demonstrated or had the potential of demonstrating suicide or suicide related behavior. “Suicide gesture” is any act, inclination, hint, verbal threat, explicit or implicit that could suggest a risk for a suicide attempt. This includes features or manifestations of the patient that would indicate suicidal ideation. As a clinician and an expert in drug safety, it is my opinion that the Neurontin labeling adequately conveyed necessary information to prescribers regarding risks and benefits of Neurontin, and suicide behavior and depression were appropriately described in the label.

On October 20, 2005, the FDA sent an e-mail, which is **Exhibit 7201**, requesting that Pfizer make a few minor changes to the Neurontin label. Specifically, the FDA asked that Pfizer delete “suicidal” and “suicide gesture” and add “suicide attempt” as an infrequent event and “suicide” as a rare event in the epilepsy section. In an October 27, 2005 e-mail from the FDA, which is labeled **Exhibit 7202**, the agency explained that “suicidal” should be deleted because the FDA viewed it as an adjective and thought it unclear without any noun following it. As for “suicide gesture,” the agency said it was a less clear term than “suicide attempt.” As reflected in

Exhibit 7203, which is an e-mail Pfizer sent to the FDA on November 18, 2005, the company explained that “suicide gesture” was not intended to encompass suicide attempt, but instead reflected self-injurious behavior associated with no intent to die. As further explained in the e-mail, “suicide gesture” describes behavior that is intended to effect change in others or the environment or intended to relieve distress, such as superficial cuts or scratches, hitting/banging, or burns. The term “suicidal,” which had been included in the Neurontin label since 1993, was taken from Warner-Lambert’s modified COSTART dictionary and included “attempted suicide” and “suicide ideation.” A few days later on November 22, 2005, the FDA sent the company another e-mail, which is labeled **Exhibit 7204** and shown on this slide [**SHOW POWERPOINT HERE (FDA’S MINOR LABELING CHANGE REQUEST)**], advising that the company should “proceed with the minor labeling changes.”

I have also reviewed the expert reports and materials relied upon by plaintiff’s expert Dr. Cheryl Blume. I have numerous criticisms of Dr. Blume’s methodologies and conclusions that are detailed in my reports. The key criticisms, in my opinion, are currently being displayed and are the following: [**SHOW POWERPOINT HERE (TOP CRITICISMS OF BLUME)**]

- (1) The conclusions of the FDA clinical reviewers and the Peripheral and Central Nervous System Advisory Committee indicate that no evidence for an increased risk of suicidality or depression existed based on data from the Neurontin clinical trials in epilepsy.
- (2) FDA’s initial labeling decision not to include a warning for suicidal behavior and depression was confirmed repeatedly in subsequent analyses of the Neurontin safety data.

- (3) FDA did not find any individual dechallenge-rechallenge observations sufficient to override the statistically comparison of adverse events reported by patients in the treatment and placebo groups.
- (4) Dr. Blume's report repeatedly aggregates or "lumps" multiple adverse events into a category called "Psychobiologic Adverse Events" - there is no explanation or medical basis provided in the Blume report of any medical or physiological semantic relationship between this aggregate concept and the concept of suicidality, nor would she by virtue of her qualifications, including her lack of medical training, be able to provide any.
- (5) Dr. Blume's report incorrectly defines the concept of a proportional reporting ratio and subsequently misapplies it in graphical representations. The Blume report also fails to call out the widespread recognition of the limitations of this approach articulated by Dr. Strom as well as by Dr. Greenland.
- (6) Dr. Blume highlights raw numbers of adverse event reports, but she does not calculate rates which provide a measure of risk and are necessary to identify excess risk. Nor does she compare rates among comparator groups. She does not compare the rate of suicide in Neurontin patients with those of patients receiving placebo.
- (7) FDA's meta-analysis in 2008 and the subsequent requirement of a class label does not indicate that prior decisions concerning the Neurontin label were wrong. In fact, the Neurontin data analyzed by FDA in 2008 would not suggest the need for a warning.

Before concluding, I want to show you a slide that shows a time-line of the safety data sent to **FDA. [SHOW POWERPOINT HERE (SAFETY DATA SENT TO FDA)]**. Starting in 1992, the company submitted safety data to FDA in the Epilepsy ISS. Safety Updates were

submitted to FDA between May of 1992 and December of 1993. Following the initial approval of Neurontin in 1993, the company submitted safety data with the 1999 and 2001 supplemental applications. In response to requests from FDA, the company submitted analyses of postmarket and clinical trial suicidality data in 2004 and 2006. In April of 2004, FDA requested and the company submitted 1- and 5-year PSURs, which summarize all safety data for Neurontin.

In conclusion, as I stated earlier my opinions in this case to a reasonable degree of medical and scientific certainty are that: **[SHOW POWERPOINT HERE (DR. RUGGIERI'S OPINIONS)]**

- (1) Pfizer and Warner-Lambert acted reasonably and complied with regulatory requirements in monitoring the safety of Neurontin.
- (2) The information available to Warner-Lambert and Pfizer has consistently failed to support an association or a signal of increased risk for depression or suicidal behaviors.
- (3) No signal existed that would raise safety issues concerning suicidal behaviors and the off-label use of Neurontin, including in neuropathic pain populations.
- (4) The Neurontin labeling adequately conveyed necessary information to prescribers regarding the risks and benefits of the medicine.